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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/068,293	Applicant(s) Sandalon et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *May 6, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-46* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-46* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Drawings

1. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

2. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

3. The use of the trademark Baculogold has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

4. Claim 1 is objected to because of the following informalities: in section "f)", after the semicolon, the portion which begins with "and further..." should be set off as a separate section. Appropriate correction is required.

5. Claim 18 is objected to because of the following informalities: line 3 of section "b." recites "recombinant SV40 viruses". In order to make the appropriate antecedent connection to the preamble which recites in line 1, "SV40 viruses", "SV40 viruses" should be amended to read "recombinant SV40 viruses". Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-17 and 41-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claim is drawn to a construct of SV40 viruses or pseudoviruses comprising exogenous nucleic acid and at least one pure or semi-purified SV40 capsid protein wherein the exogenous nucleic acid or an exogenous protein is therapeutic and therapeutic methods of using the construct. While applicants have shown *in vitro* constructs, they have not demonstrated *in vivo* therapeutic use for the construct. In order to do so, undue experimentation is required. Whether undue experimentation is needed is not based on a single factor, but rather a conclusion

reached by weighing many factors. Many of these factors have been summarized in *In re Wands*, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988).

The Wands factors as they apply to the instant claimed invention are as follows:

a- The quantity of experimentation necessary to reduce the instant claimed invention to practice would involve experimentation with SV40 constructs *in vivo* to demonstrate therapeutic activity of the constructs.

b- Applicants have provided guidance and working examples of the constructs *in vitro* and no working examples and only limited prophetic guidance for therapeutic use of the constructs *in vivo*.

c- The nature of the invention is complex. Gene therapy is a new and developing art as recited in Marshall in the section titled "The trouble with vectors", and at page 1054, column 3, and at page 1055, column 3. The problems of gene delivery, gene targeting to reach the intended host cell, and then to reach the intracellular target are not yet solved, as taught in Verma et al. (see especially page 239, column 3, the box titled "What makes an ideal vector?" and page 242).

d- The prior art taught by Orkin et al. (see especially the section on "Gene transfer and expression" and "Gene therapy in man status of the field") described many problems in the developing field of gene therapy. Recited problems include: lack of efficacy, adverse short term effects and limited clinical experience, the inability to extrapolate experimental results and unreliability of animal models. Problems with the vector include: host immune response to the

vector and the expressed product, difficulty of targeting the vector to the desired site, transient expression of the gene of interest and low efficiency of delivery of the vector to the targeted site.

e- The state of the art as taught by Verma et al., which states "the problems - such as the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable problems" and Anderson, W. F. (see page 25, top of column 1), which states "[e]xcept for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease".

f- Therefore, given the analysis above, it must be considered that the skilled artisan would have needed to have practiced considerable non-routine, trial and error experimentation to enable the full scope of the claims.

8. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not sufficiently describe the possible inventions drawn from the claim. There is no information given regarding the structures of a gene that may suggest potential antisense oligonucleotides which may be created or found. There are virtually an infinite number of such antisense oligonucleotides of all potential target nucleic acids or their complements, and no disclosure as to which portions of the nucleic acids are structurally important; therefore, the

specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of any of these compounds at the time of filing of the instant application.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 3, 4, 7, 9, 10, 12, 25, 27-28, 32, 35, 37, 43 and 45 (and all dependent claims) are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 recites the phrase "capable of" which renders the claim(s) indefinite because the capacity of a compound to perform some function is merely a latent characteristic of said compound and said language carries no patentable weight. See MPEP § 2173.05(b), (d) and (g).

12. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term "replication of a said exogenous protein" in claim 1 is used by the claim to mean "that a protein can be replicated," while the accepted meaning is "that a nucleic acid can be replicated".

13. Claim 1 recites the limitation "exogenous protein" in line 26. There is insufficient antecedent basis for this limitation in the claim.

14. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "at least two semi-purified or pure SV40 capsid proteins", and the claim also recites "at least one semi-purified or pure SV40 capsid proteins" which is the narrower statement of the range/limitation.

15. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely

exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 4 recites the broad recitation "a mixture of three semi-purified or pure SV40 capsid proteins", and the claim also recites "at least one semi-purified or pure SV40 capsid proteins" which is the narrower statement of the range/limitation.

16. Claims 7, 10, 12, 25, 28 and 32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: the claims recite that DNA which may be contained in a cell, where the DNA encodes a therapeutic protein which is not made or contained in the cell. It is not clear if the claim intends that the protein is not made in the cell when the DNA is contained in the cell, or if the protein is not normally made by the intended host cell.

17. The term "abnormally low amount" in claims 7, 10, 12, 25, 28 and 32 is a relative term which renders the claim indefinite. The term "abnormally low amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art

would not know when the characteristics of the protein in question stopped being an "abnormally low amount".

18. The term "defective form" in claims 7, 10, 12, 25, 28 and 32 is a relative term which renders the claim indefinite. The term "defective form" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know when the characteristics of the protein in question stopped being a "defective form".

19. The term "physiologically abnormal or normal amount" in claims 7, 10, 12, 25, 28 and 32 is a relative term which renders the claim indefinite. The term "physiologically abnormal or normal amount" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Without proper guidance as to the metes and bounds of the claims, one of ordinary skill in the art would not know when the characteristics of the protein in question stopped being a "physiologically abnormal or normal amount".

20. Claims 9 and 27 recite the limitation "SV40 derived". One of ordinary skill in the art would not know how to interpret the metes and bounds of this limitation. A derivation of a virus may be closely patterned after the subject virus or may be very loosely patterned after the subject virus, such that it may bear no resemblance or form recognizable as the subject virus which may be chemically and/or biologically totally unrelated in function or form to the subject virus.

21. Claim 35 recites the limitation "recombinant" in line 15. There is insufficient antecedent basis for this limitation in the claim.

22. Claims 43 and 45 recite the limitation "SV40 viruses or pseudoviruses" in lines 5 and line 3, respectively. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

23. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

24. Claims 18, 19, 21, 22, 24, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Forstova et al (of record).

Forstova et al. taught (see especially the abstract, overview summary, the introduction, the figures and the discussion) a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. The pseudoviruses were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear. The pseudovirus was suggested to be used as gene therapy delivery vehicle, and the pseudovirus was purified away from non-packaged protein. Forstova et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

25. Claims 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Christensen et al (of record).

Christensen et al. taught (see especially the abstract, the introduction, the figures, pages 438-439 and the discussion) a method of construction of SV40 viruses and pseudoviruses comprising a semi-purified or pure SV40 capsid protein and at least one other SV40 protein, where the capsid was assembled and then the exogenous DNA was added to give pseudoviruses. The pseudoviruses were treated with nuclease to remove non-packaged DNA. The DNA was circular or linear. Christensen et al. taught each and every aspect of the instant invention, thereby anticipating Applicant's invention.

Claim Rejections - 35 USC § 103

26. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

27. Claims 23, 25-28 and 31-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forstova et al. or Christensen et al. (above) in view of Carswell et al. (of record), Oppenheim et al. (J. Virol. Vol. 66, 1992, of record) and US Pat No. 5,863,541.

Forstova et al. or Christensen et al. taught the invention described above.

Forstova et al. or Christensen et al. did not teach the exogenous nucleic acid may be RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone, which may be a therapeutic protein

US Pat No. 5,863,541 taught (see especially the abstract, the summary, column 5 and the claims) the production of AAV capsid proteins which were allowed to self assemble into capsids and then the exogenous nucleic acid was added to give pseudoviruses. The exogenous nucleic acid may be DNA, RNA, or antisense, and/or may encode a protein, receptor, structural protein, regulatory protein or hormone, which may be a therapeutic protein. The host cell may be a human cell.

Carswell et al. taught (see especially the abstract) the advantage of combining an SV40 agnoprotein with SV40 capsid proteins to facilitate the assembly of capsids.

Oppenheim et al. (see especially the abstract) the advantage of combining an SV40 ori with SV40 capsid proteins to facilitate the assembly of capsids.

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. with the method of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because the capsids proteins of US Pat No. 5,863,541 were assembled in a like manner to the instant claimed invention, and inclusion of nucleic acids which encode various therapeutic entities is an obvious extension of the gene therapy teachings of Forstova et al. or Christensen et al. and because the AAV capsids of US Pat No. 5,863,541 were used for the same purpose and

demonstrated the generally accepted practice of making pseudovirions for delivery of exogenous nucleic acids and proteins to cells. It is assumed that the making of AAV pseudovirions and SV40 pseudovirions is equivalent for the purpose of delivering exogenous nucleic acids and proteins to cells. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of facilitating the assembly of SV40 capsid proteins into SV40 capsids.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. with the method of US Pat No. 5,863,541, Carswell et al. and Oppenheim et al. to produce the instant invention because US Pat No. 5,863,541 recited at column 3, lines 11-13, "[m]olecules which may be associated with or encapsidated into capsids include DNA, RNA, proteins, peptides, small organic molecules, or combinations of the same.", continuing at lines 26-27, "[t]his system may be particularly advantageous in AAV gene delivery systems...". Then at column 4, lines 21-23, "[m]ethods for the *in vitro* construction of AAV capsids and for the *in vitro* packaging of these capsids are also provided." While Forstova et al. recite at the last 3 lines of the abstract, "[t]he ease of production of VPI pseudocapsids, coupled with their efficient transfer of biologically useful information, should make this route of gene delivery an attractive proposition for further exploration with regard to gene therapy." Therefore, the capsids of US Pat No. 5,863,541 and Forstova et al. or Christensen et al. were intended for the same purpose, where US Pat No. 5,863,541 utilized AAV capsids and Forstova et al. or Christensen et al. utilized SV40 capsids. Carswell et al. and Oppenheim et al. merely taught well known and advantageous methods of

facilitating the assembly of SV40 capsid proteins into SV40 capsids. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Forstova et al. or Christensen et al. with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541.

28. Claims 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forstova et al. or Christensen et al. with Carswell et al., Oppenheim et al. and US Pat No. 5,863,541. as applied to claims 23, 25-28 and 31-38 above, and further in view of Szczylik et al. (of record).

The claims are rejected for all the reasons above and because Szczylik et al. taught (see especially the abstract, materials and methods and the figures) an antisense oligonucleotide to *bcr/abl.*

It would have been obvious to one of ordinary skill in the art at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No. 5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention because Forstova et al. or Christensen et al. with US Pat No. 5,863,541 taught the inclusion of antisense oligonucleotides in the assembled SV40 pseudocapsids. The antisense oligonucleotide of Szczylik et al. being an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention.

One of ordinary skill in the art would have been motivated at the time of making the instant invention to modify the method of Forstova et al. or Christensen et al. and US Pat No. 5,863,541 with the antisense oligonucleotide of Szczylik et al. to produce the instant invention because the antisense oligonucleotide of Szczylik et al. was an obvious choice of one of the many antisense oligonucleotides within the purview of one of ordinary skill in the art at the time of the instant invention. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Forstova et al. or Christensen et al. with US Pat No. 5,863,541 and with Szczylik et al.

Conclusion

29. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.

Examiner

August 10, 1999

DAVID GUZO
PRIMARY EXAMINER